Management of recurrent apthous stomatitis-current trends & perspective

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Abstract
Recurring oral ulcers are among most common oral disease encountered by oral physicians in day to day practice.Recurrent apthous stomatitis (RAS) is a common disorder characterized by recurring ulcers confined to the oral mucosa with no other signs of systemic diseases. It affects approximately 20% of general population. Clinically it is classified as minor ulcers, major ulcers and herpetiform ulcers. This article insights the current trends in management of this commonly occurring disease.

Keywords: Recurrent Aphthous Stomatitis, Oral ulcers, Etanercept, Autoimmune diseases.

Introduction
Apthous word is derived from the greek word aptha meaning "eruption" or "ulcer". Recurrent is the word added to name because of the nature of disease, occurring repeatedly in oral cavity at intervals. The etiology behind this disease is still unclear. Cell mediated immune response plays pivotal role in immunopathogenesis of apthous ulcer.[1] There are at least 4 episodes of the disease per year.[2] Prevalence is found to be higher in developed countries irrespective of age, race or geographic distribution.[3]

Sometimes it is related to systemic diseases like Crohn's disease and Behcet's disease, adversely influencing the quality of life of patients.[4] Certain HLA findings in some patients strengthens role of genetic predisposition.[5] Some patients report of prodromal burning sensation 2 hrs to 2 days before the appearance of ulcer.[6] Some predisposing factors are associated with RAS like trauma, vitamin deficiencies, stress, hormonal influences, immunologic parameters and microbial load.[6,7]

Initiation of cascade of inflammatory cytokines against oral mucosa triggerred by predisposing factors results in activation of T-lymphocytes and leukocyte chemotaxis.[8] Production of cytokines like interferon-alpha (INF-α), interleukin-2, interleukin-12 and tumor necrosis factor-alpha (TNF-α) from T-helper cells further contributes to the immune response. Some evidences of presence of auto-antibodies against oral mucosa are also found.[9]

Current trends in management of RAS
Clinical appearance of RAS is as single or multiple painful shallow round ulcers with pseudomembranous centre and erythematous margin. RAS has 3 subtypes; recurrent apthus major, minor and herpetiform. It mostly involves non keratinizing oral mucosa like buccal mucosa, labial mucosa and tongue.[1,6] Till today it is difficult to catch whether a similar pathogenesis exists between RAS associated with other systemic disease and RAS unassociated with any systemic disease.[10] A study by Ozyurt K et al., reveals that the serum interferon gamma, alpha-enolase levels, interleukin-1, interleukin-13, interleukin-18 were found to be in increased concentration in patients with Behcet's disease as well as RAS in comparison to healthy controls.[10,11] There is no specific diagnostic test. The main basis of diagnosis is a meticulous patient history and gross clinical examination. Family history also plays a vital role. While examining the patient we must give concern to the size, number, location and frequency of ulcers. To have an idea about any underlying systemic cause we can run certain tests like estimation of full blood count, hemoglobin, C-reactive protein, erythrocyte sedimentation rate, vitamin B12 level, anti-endomysial and anti-gliadin autoantibodies.[12]

Our treatment must aim at reducing the duration and frequency of ulcers to improve the level of well being for the patient. Different patient respond differently to the various treatment regimens. Therapeutic approach may be topical or systemic as per the severity of disease. Several trials are undertaken to determine the best treatment approach for RAS. Antibiotic mouthrise are prescribed in mild initial cases. Chlorhexidine 0.2% mouth rinse or 1% gel formulation is known to reduce the duration and severity of disease.[13] 5 ml of minocycline, 0.2% mouthrinse in aqueous solution when rinsed 6 hourly provided early relief from RAS.[14]

Other topical treatments include application of dexamethasone ointment (5mg) on ulcers 3 times a day post meal for 5 days accelerated healing process[15]. Adhesive pellicles (2mg) of amelexanox or 5% paste formulation when applied 8 hourly, reduced pain intensity and size of ulcers.[16,17] Reduction in pain was noted from day 1 after chemical cauterization of ulcer with siver nitrate pencil (1-2%).[18,19] We all know LASERS are paving their way as latest diagnostic and treatment modality. As far as RAS treatment is concerned Nd:YAG laser and CO2 laser treatment

presented with immediate relief.[20,21] Topical treatment modalities mentioned above have been proved to be effective in minor form of disease. But RAS with more recurring episodes and higher severity may need systemic therapy. Vitamin B supplementation accelerates the healing process. Systemic medications includes various drug regimens. Thalidomide 100mg oral when given daily for 15 days led to complete remission of RAS.[22] But it is contraindicated in pregnancy and bears numerous side effects like headache, xerostomia, constipation. Colchicine 0.5mg daily oral dose for 3 months helped in reduction in number of ulcers and intensity of associated pain.[23] 400 mg of pentoxyfylline taken orally 3 times a day causes reduction in size of ulcer.[24] Another drug in this row is clofazimine. When it was given at a dose of 100mg orally on alternate days, increased disease free intervals.[25] But clofazimine has certain cutaneous side effects.[26]

Systemic corticosteroids are well accepted treatment modalities in RAS major cases. 25mg daily administration of predinisone for 15 days followed by gradually tapered maintenance dose over next 45 days resulted in rapid healing along with decreased frequency of ulcers.[27] Systemic administration of corticosteroids have a series of adverse reactions on body which must be kept in concern. Montelukast 10mg/day when given for 1 month and alternate day for next 30 days resulted in resolution of ulcers.[27] Dapsone 100mg daily orally is also a treatment of choice.[28] Zinc sulfate 150 mg daily oral dose for 12 weeks reduced the number and size of ulcers without any side-effect.[29] Subantimicrobial dose of doxycycline (20mg) BD increased disease free periods.[30] Rebamipide 100 mg thrice in a day orally for 7-14 days caused reduction in number of ulcers and pain intensity.[31] A randomized controlled trial by Volkov I et al revealed that a daily dose of vitamin B12 (1000mcg) sublingually for 6 months decreased pain intensity and number of ulcers in RAS.[32] Levamisole 150mg/day oral when given on 3 consecutive days every fortnight also gave positive treatment outcomes.[33]

Novel therapeutic regimens

Biologic agents are the latest trends in treatment of apthus ulcers. They block certain immunologic or pathophysiologic pathways of disease. They have targeted approach. Either they are immunosuppressive or anti-inflammatory in action[34]. Some names in this queue are etanercept, adalimumab, infliximab and IFN-gamma.

Structurally, etanercept is a dimeric fusion protein comprising the extracellular portion of human TNF receptor (p75) coupled to the Fc fragment of human IgG. It is a recombinant TNF soluble receptor. It competitively inhibits the binding of TNF to TNF receptors thereby preventing TNF-mediated cell responses[35]. It is given subcutaneously, at a dose of 25mg two times a week[36]. It can be self administered by the patient. Studies suggest significant improvement in refractory cases as well as complete remission in some.[35-38]

A murine monoclonal antibody named infliximab acts against TNF-a. Infliximab when administered in a dose of 3-5mg/kg intravenously every 2-6 weeks showed early healing and complete remission within 7-10 days in old RAS cases resistant to other treatment modalities.[39-44] Adalimumab is a human monoclonal antibody. It binds to TNF-α resulting in inhibition of the activity of TNF-α. It achieves higher affinity as compared to infliximab and etanernept.[45] It has an advantage of having fewer side effects. Complete resolution or remission was found in several study cases of RAS with associated systemic dirsease.[45-49] INF-α plays vital role in immune response. It helps in clearance of all foreign antigens and maintaining, immunological memory. Treatment with a low dose of INF- α causes de-acceleration of delayed-type hypersensitivity.[50] Topical,[51] oral[52,53] and subcutaneous[54,56] INF-α therapy diminished oral aphthous lesions.

Conclusion

Taking a thorough patient history and performing meticulous oral examination are key to sound diagnosis and treatment planning of recurrent apthous stomatitis. There is a strong need to rule out whether RAS is associated with any underlying systemic disease that need to be managed. Elimination of predisposing factors is mandatory for successful treatment. More studies need to be conducted to find a definite treatment protocol for RAS. There are several treatment options to which different patient responds differently. Biologic agents are recent trends that have been used to treat apthous ulcer as well as they are a ray of hope for the old refractory cases of RAS.

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